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INTEGRATED STUDY MASTER'S THESIS

# Follow-Up of Superficial Urothelial Carcinoma With Non-Invasive Diagnostic Tools. Literature Review

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**Abstract**

Superficial urothelial carcinoma (UC), or non-muscle-invasive bladder cancer (NMIBC), represents the predominant form of bladder cancer which is associated with a significant risk of recurrence and progression. Conventional surveillance techniques, such as cystoscopy and cytology, continue to be the benchmark in follow up in affected patients; however, they are invasive, expensive, and uncomfortable. This literature review examines both conventional and novel tools for NMIBC surveillance, focusing on non-invasive urinary biomarkers, imaging modalities, and individualized risk stratification models. Recent advancements in molecular diagnostics such as DNA methylation assays, mRNA panels, and proteomic profiling display promising diagnostic precision and the potential to reduce dependence on repeated invasive procedures. The incorporation of patient-centered approaches, such as lifestyle modifications and systemic inflammatory indicators, enhances the developing framework of NMIBC management. This review seeks to advocate for a transition to a more personalized, minimally invasive, and cost-effective approach for monitoring NMIBC patients through a critical analysis of existing evidence and research.

Key Words: Bladder Cancer, Superficial Urothelial Carcinoma, NMIBC, NMIBC Surveillance, TURBT, Cystoscopy, Cytology, Urinary Biomarkers

**Abbreviations**

- 16-MDCT: 16-Multidetector Computed Tomography
- AFM: Afamin
- ALDH1: Aldehyde dehydrogenase 1 family, member A1
- APOA1: Apolipoprotein A1
- APOL1: Apolipoprotein L1
- AS: Active Surveillance
- ATR-FTIR: Attenuated Total Reflectance - Fourier Transform Infrared Spectroscopy
- AUC: Area Under the Curve
- AUROC: Area Under Curve : Receiver Operating Characteristics
- BCG: Bacillus Calmette-Guerin
- BTA: Bladder Tumor Antigen

- CCI: Charleston Comorbidity Index
- CDC5L: Cell Division Cycle 5-Like Protein
- CIS: Carcinoma In Situ
- CRP: C-reactive Protein
- CSTB: Cystatin B
- CT: Computed Tomography
- CUETO: Club Urologico Espanol de Tratamiento Oncologico
- DDR: DNA Damage-Repair
- DCE: Dynamic Contrast-Enhanced
- DLB: Dementia with Lewy Bodies *(likely not relevant here, possibly a mistake)*
- DWI: Diffusion-Weighted Imaging
- EAU: European Association of Urology
- EGFR: Epidermal Growth Factor Receptor
- ELISA: Enzyme-Linked Immunosorbent Assay
- EMA: European Medicines Agency
- EORTC: European Organisation for Research and Treatment of Cancer
- FDA: Food and Drug Administration
- FGFR3: Fibroblast Growth Factor Receptor 3
- FGB: Fibrinogen Beta Chain
- FISH: Fluorescence In Situ Hybridisation
- GWAS: Genome-Wide Association Studies
- HC: Healthy Controls
- HER2: Human Epidermal Growth Factor Receptor 2
- HG: High-Grade
- ITIH: Inter-Alpha-Trypsin Inhibitor Heavy Chain
- KRT7: Cytokeratin 7
- LC-MS: Liquid Chromatography–Mass Spectrometry
- LG: Low-Grade
- Ln-γ2m: Laminin-γ2 Monomer
- mRNA: Messenger Ribonucleic Acid
- miRNA: Micro Ribonucleic Acid
- MIBC: Muscle-Invasive Bladder Cancer
- mpMRI: Multiparametric MRI
- mTOR: Mammalian Target of Rapamycin
- NBI: Narrow-Band Imaging
- NIR-PIT: Near Infrared Photoimmunotherapy
- NLR: Neutrophil-to-Lymphocyte Ratio
- NMP22: Nuclear Matrix Protein Marker

- NMIBC: Non-Muscle-Invasive Bladder Cancer
- NPV: Negative Predictive Value
- OTX1: Orthodenticle Homeobox1
- PDD: Photodynamic Diagnosis
- PIT: Photoimmunotherapy
- PSEN1: Presenilin 1 *(note: not in original list but often used with HER2 etc.)*
- PUNLMP: Papillary Urothelial Neoplasm of Low Malignant Potential
- RC: Radical Cystectomy
- REG1A: Regenerating Family Member 1 Alpha
- SKP2: S-Phase Kinase-Associated Protein 2
- SNP: Single Nucleotide Polymorphisms
- SVV: Survivin
- TIP30: Tat-Interacting Protein 30
- TNM: Tumor, Node, Metastasis (staging system)
- TPS: The Paris System
- TUR: Transurethral Resection
- TURB: Transurethral Resection of Bladder Tumor
- UBT: Urinary Biomarker Test
- uCRN: Urine Creatinine
- ucfDNA: Urinary Cell Free DNA
- UC: Urothelial Carcinoma
- US: Ultrasound
- WCRF/AICR: World Cancer Research Fund/American Institute for Cancer Research
- WLC: White Light Cystoscopy

## 1. Introduction

This literature review will examine the current strategies and emerging approaches in the follow-up of superficial UC, also referred to as NMIBC. In the first chapter, to provide a foundation for understanding NMIBC, the topics of bladder cancer, including its epidemiology, clinical presentation, risk factors, and histopathological features, will be covered. These elements are essential for understanding the challenges and considerations associated with the management and follow-up of NMIBC. In the second chapter, the standard surveillance methods in NMIBC, such as cystoscopy and cytology, will be discussed. This subsection will transition the thesis into chapter 3, where the literature review of non-invasive follow-up of NMIBC will begin. In that chapter, traditional urinary biomarkers will be covered. Chapter 4 will be focused on a revision of emerging biomarkers and urinary proteomics. Imaging methods for NMIBC will be examined in chapter 5. In chapters 6 and 7, risk models and AS techniques will be highlighted. Finally, this thesis will finish by addressing the role of lifestyle modifications and systemic markers in the follow-up of superficial UC.

Bladder cancer ranks among the top ten most commonly diagnosed cancers worldwide, with an annual global incidence exceeding 500,000 cases and over 200,000 related deaths, as reported by the WHO (1). Beyond its clinical burden, the disease poses a substantial economic impact, with direct medical expenditures in the United States alone estimated at over $3.7 billion annually (2). Bladder cancer more commonly affects men, as they are four times more likely to develop this disease than women (3) Finally, the disease is primarily a cancer affecting adults who are 60 and older (3) .

The predominant initial symptom typically presented by patients is gross or microscopic hematuria (3). More than one third of patients who have visible blood in the urine and slightly over 10% of those with microscopic hematuria will eventually be diagnosed with bladder cancer at some point in their lives (3). Additional symptoms may include painful urination, increased frequency of voiding, a pelvic mass, and constitutional symptoms such as fatigue and weight loss (3).

It is currently estimated that about 75% of patients with bladder cancer present with the malignancy confined to the mucosa, such as in stage Ta, CIS, or to the submucosa in the T1 stage (4). In patients under the age of 40, those rates are even higher (4).

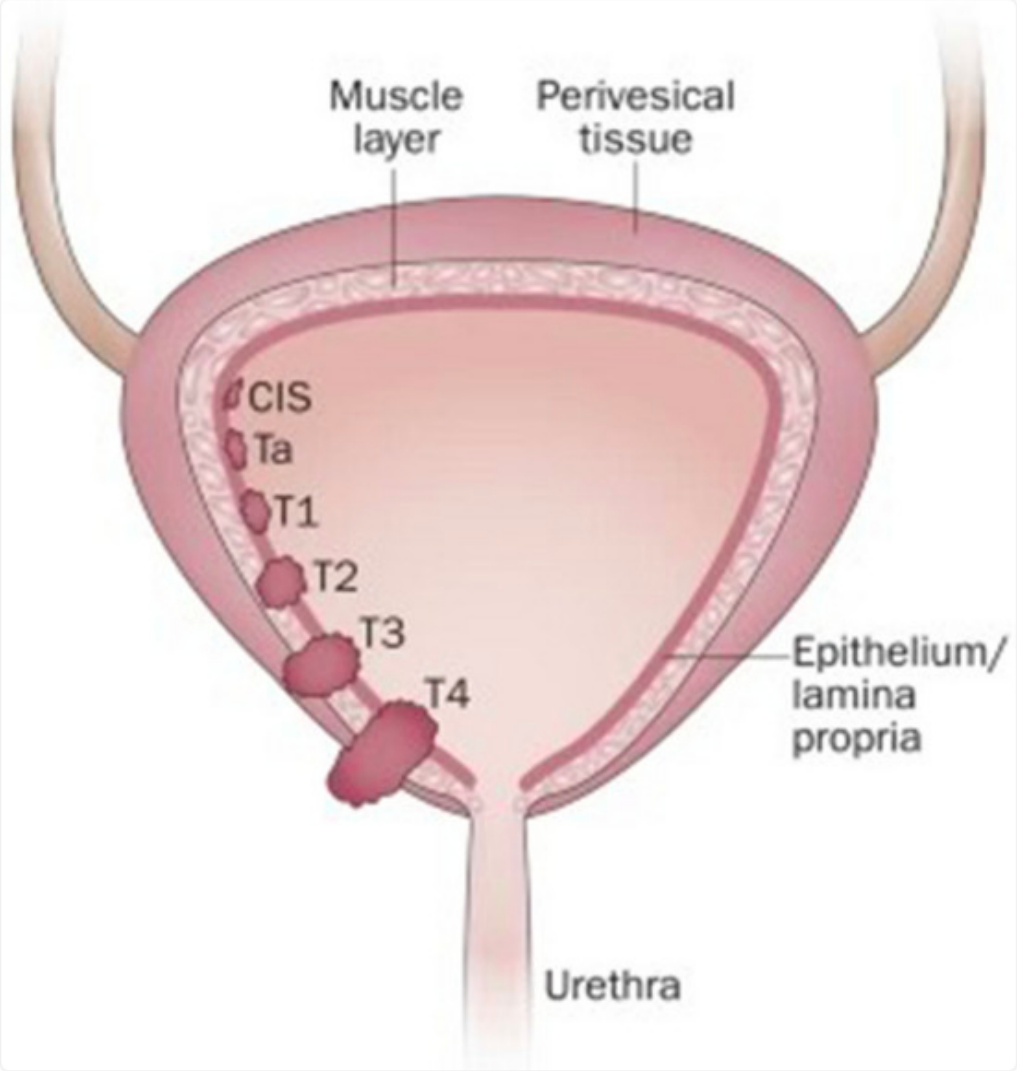


Image: Visualizing bladder Cancer Staging (5)

Many risk factors for bladder cancer exist. The single most important risk factor is smoking, with about 50% of bladder cancer cases resulting from it (6). People who currently smoke have 3.47 times the risk of developing bladder cancer compared to people who have never smoked (6). In second place, approximately 10% of all bladder cancers occur due to occupational exposure to carcinogens such as aromatic amines, polycyclic aromatic hydrocarbons, heavy metals, and

mixed compounds (7). Genetics also play a role in bladder cancer, as those with first-degree relatives with the malignancy are two times more likely to develop the cancer themselves (8). However, no major gene is involved in bladder cancer development (8). Additionally, the chronic use of a urinary catheter and previous chemotherapy, especially with cyclophosphamide or ifosfamide, irritative urinary symptoms, older age, and male sex are important risk factors (3). Lastly, other risk factors include exposure to external beam radiation in patients with pelvic cancer, who are subsequently at a higher risk of developing secondary bladder cancer (9), and infection with Schistosomiasis, which is prevalent in countries like Egypt (10).

The urinary bladder wall is made up of 4 different layers: mucosa, submucosa, muscularis, and serosa (3). The wall of the urinary bladder comprises four distinct layers: mucosa, submucosa, muscularis, and serosa (3). The mucosa comprises a stratified, uniform, non-squamous epithelium, known as urothelium, that is 3 to 6 cells thick (3). Large umbrella cells are located atop the mucosa, accompanied by an additional superficial glycosaminoglycan layer (3). This layer serves as a protective barrier, shielding the bladder from irritating urinary chemicals (3). Basal cells are located below the umbrella cells, with intermediate cells sandwiched in between (3). Bladder cancer can originate from the basal cell layer, as seen in cases of CIS, MIBC, and squamous cell carcinoma, or from intermediate cells, as in NMIBC (3).

### 1.1 Brief overview of NMIBC

This subsection will discuss the classification of NMIBC in the latest EAU guidelines, addressing how the WHO classification has changed over the years and the histopathological changes observed in this malignancy Additionally, the treatment methods for NMIBC will be introduced but covered more in detail in other subsections.

Accurate classification of NMIBC is critical, as it directly influences post-treatment surveillance strategies following TUR or any radical treatment (11). NMIBC tumors are classified as stage Ta and T1, respectively, in the TNM classification system (11). Furthermore, the definition of NMIBC also includes intra-epithelial, HG tumors confined to the mucosa and classified as CIS (Tis).

Broadly speaking, NMIBC can be treated by TUR in combination with intravesical instillations (11). In approximately 10% of cases, LG papillary NMIBC can progress to a muscle-invading malignancy due to cyclin-dependent kinase inhibitor 2A loss (3). In 2004, the WHO introduced a new way to classify bladder cancers, and it includes three main types: PUNLMP, LG non-invasive cancer, and HG non-invasive cancer (11). This newer system was updated again in 2016 and 2022 and is still being used (11). Before 2004, doctors used an older WHO system from 1973 that had three grades: grade 1, grade 2, and grade 3 (11).

CIS of the bladder is a flat, superficial, HG urothelial cancer characterized by cytological atypia and nuclear anaplasia (3). Histologically, it also displays other characteristics such as loss of polarity, cellular crowding, and pleomorphism with greatly hyperchromatic nuclei and enlarged nucleoli (3). Urine cytology is positive for shed cells, resulting from the loss of cellular adhesion (3). Urothelial CIS stains positively with CK20 and p53 with excellent results (3). In 60% of the cases, CIS of the bladder recurs or progresses to a more aggressive malignancy (3). Lastly, CIS is relatively rare as a primary cancer and usually represents only 3% of all bladder cancers (3).

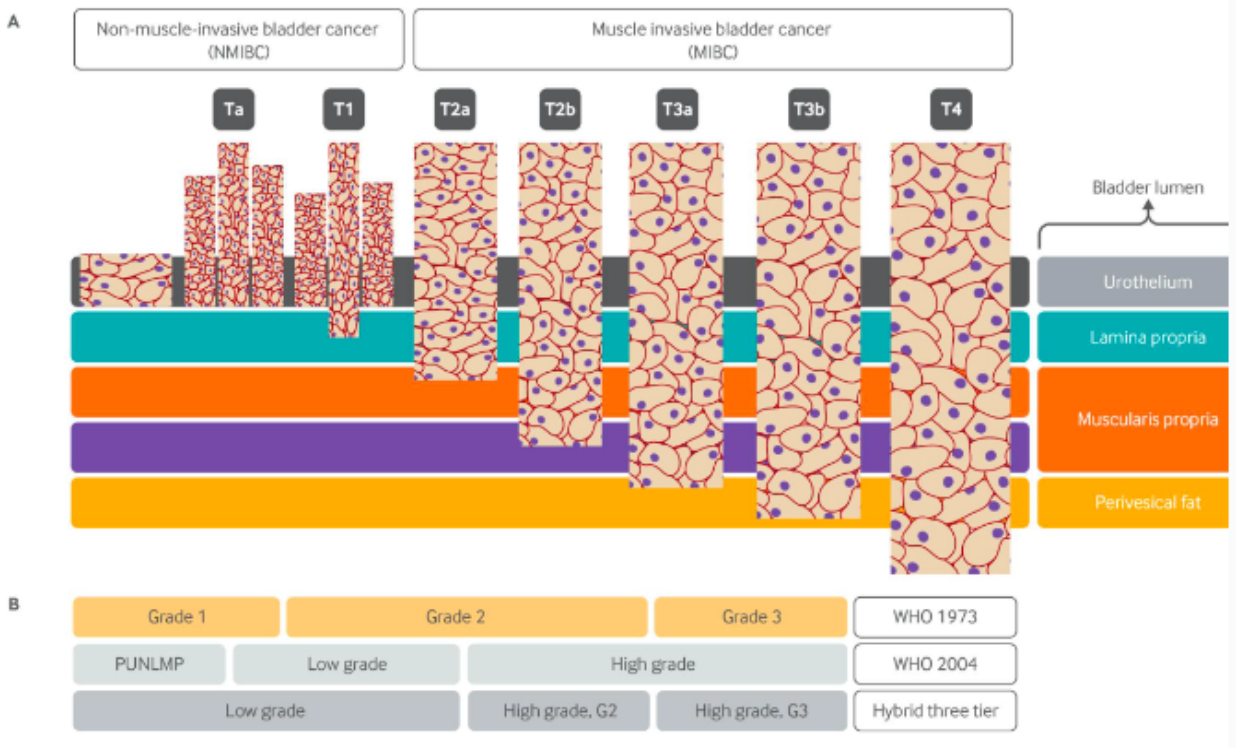


Image summarizing NMIBC classification and staging (12)

### 1.2 NMIBC treatment and importance of Surveillance

In this subsection, treatment of NMIBC will be covered in detail. Particularly, the topics of TURBT and intravesical therapies will be discussed. Understanding how this malignancy is treated allows for a more profound understanding of the role of AS in this disease. This chapter will also address the high progression and recurrence rates of NMIBC.

Per the EAU guidelines, TUR is the main procedure used to diagnose and treat NMIBC (11), and it helps determine the tumor's grade, subtype, and depth of invasion (12). In certain instances, TUR may be curative, particularly for small, low-risk tumors (12). TUR should follow a structured approach, starting with bimanual palpation and full inspection of the bladder and urethra (11). Small tumors may be excised en bloc using an electrified wire loop during the procedure, whereas larger tumors are resected in multiple fragments (11). Tumors may be excised in distinct segments, such as initially removing the tumor, followed by the underlying wall, and ultimately the margins (11).

The EAU guidelines make a few recommendations when it comes to TUR to diagnose and manage NMIBC. First, the absence of muscle tissue in the resected specimen may lead to staging uncertainty and increase the risk of incomplete removal and understaging, which is not a concern for LG Ta tumors (11). In cases of incomplete TUR, missing muscle, or T1 tumors, another TUR is recommended to detect residual disease, improve treatment outcomes, especially after BCG therapy, and give a more accurate prognosis (11).

PDD can improve tumor detection, particularly for CIS, and is beneficial when the bladder lining appears normal despite a positive cytology result from the patient (11). In patients with positive urine cytology but no visible tumor, PDD-guided biopsies from different bladder regions and the prostatic urethra should be done to rule out hidden cancer (11).

Post-TUR, patients with NMIBC are classified into low, intermediate, or high-risk categories according to tumor size, number, grade, stage, recurrence rate, presence of CIS, and prostatic urethra involvement (12). Individuals in the low-risk category may require only TUR and vigilant observation if the tumor has been entirely excised (12). In addition, for such patients, a single immediate dose of intravesical chemotherapy after TUR is strongly recommended (11). If chemotherapy is unfeasible, bladder irrigation with saline or water may be contemplated (11).

Small, LG recurrent tumors can often be managed with in-office fulguration or AS in selected patients (11).

Follow-up generally entails routine cystoscopy, starting three months post-surgery, subsequently at twelve months, and then for extended intervals for a duration of up to five years (12). Understanding the tumor's behavior during the initial TUR is crucial as up to 20% of T1 tumors may actually be muscle-invasive (T2), even when muscle tissue was seen in the specimen, and up to 40% if muscle was missing (12). Moreover, even if staging is correct, the tumor may still not be fully removed due to factors like its size, the number of tumors, or difficult localization of the tumor, leading to a 50% chance of incomplete resection (12). Although TUR remains a gold standard for the evaluation and management of bladder cancer and quality of resection has a direct impact on patient outcomes, it has several limitations, with the most important being high recurrence and progression rates (13).

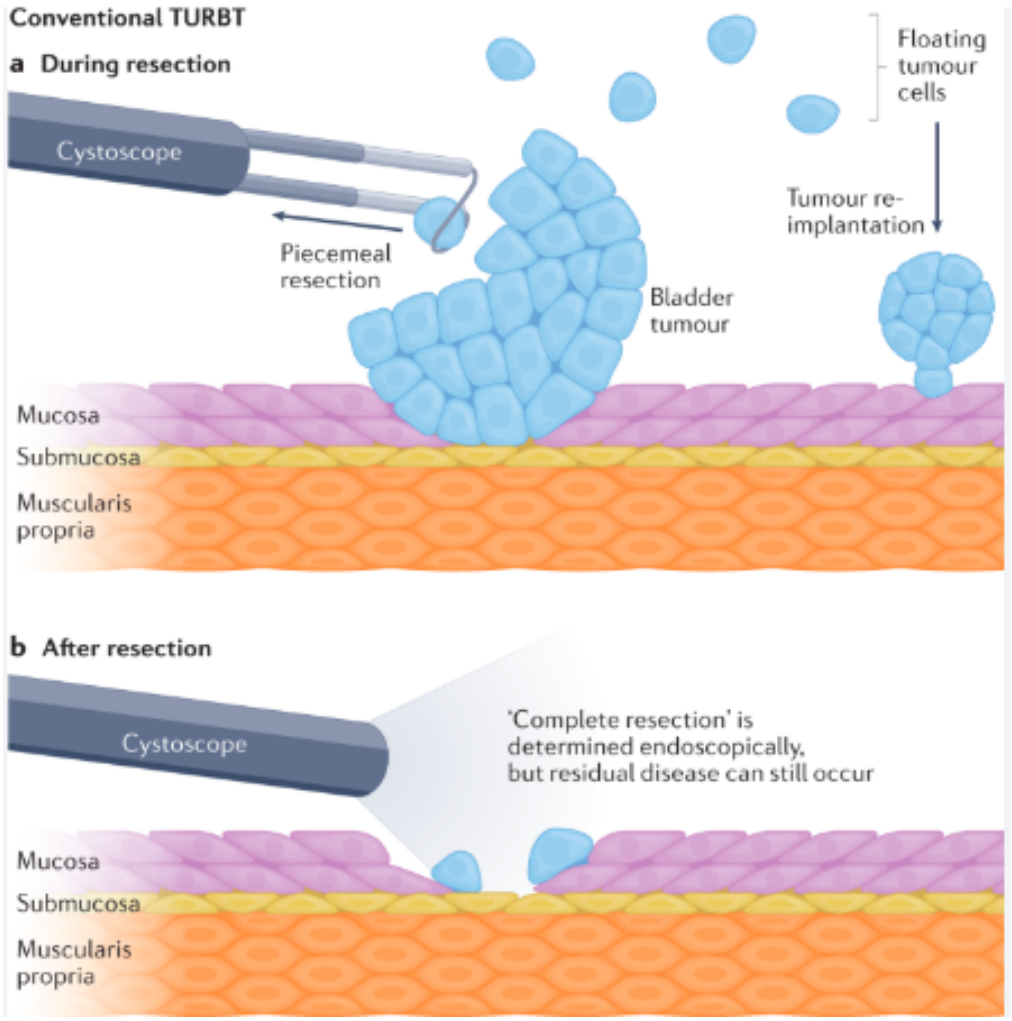

Image: Highlighting how tumor resection with TUR may still leave residual cells and other tumors intact, leading to disease recurrence/progression (14)

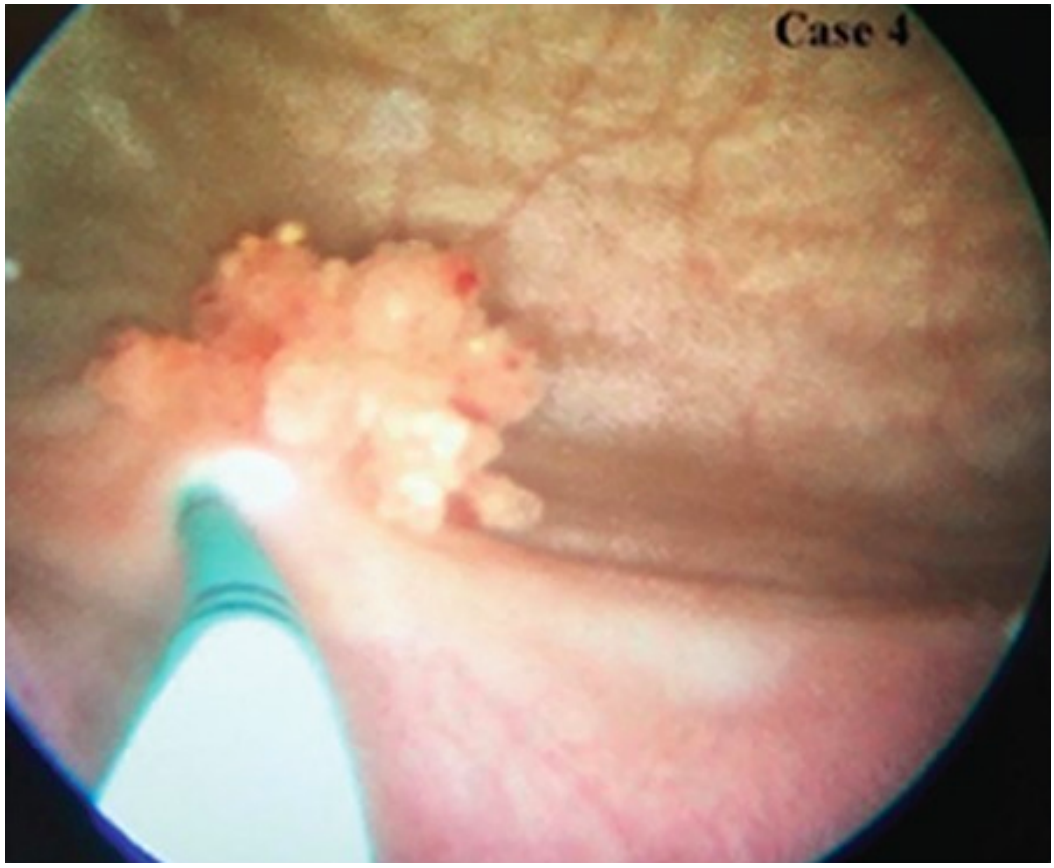


Image: Perioperative cystoscopic view of the urinary bladder tumor in the shape of a polypoid (15)

Chemotherapy is typically the first line treatment option for patients that have an intermediate or high-risk NMIBC (11). One year of BCG may also be an alternative (11). The choice should depend on the patient's risk of recurrence and the side effect profile of each treatment (11). In high-risk patients, full-dose BCG treatment for one to three years is advised, but RC should also be discussed (11). For those at very high risk, immediate RC may be preferred, but BCG therapy remains an option for patients who decline surgery or are not fit for it (11). BCG helps lower the chance of recurrence and progression (12). If the disease persists, worsens, or recurs during or after proper BCG treatment, the patient is considered BCG-unresponsive (12). In such cases, the most effective option for those who are fit is RC (12). Placing one dose of chemotherapy in the

bladder within 24 hours after TUR can reduce the risk of recurrence by 40% at one year and 15% at five years, especially in LG papillary tumors (12).

Accurate staging during TUR guides patient management, so a repeat TUR within 2–6 weeks is advised if the first tumor removal was incomplete, if the tumor has invaded the lamina propria (T1), or in cases of HG non-invasive disease (12). A second TUR procedure helps accurately stage the cancer and can also lower the chances of disease recurrence by 25% and progression-free survival by 14% over five years (12). This procedure is also recommended for patients with variant histologies of NMIBC if bladder-sparing treatment is being considered in their case (12).

The outlook for patients with urothelial bladder cancer depends on several factors, with the TNM stage being the most important predictor of prognosis (3). The 5-year overall survival rates vary by stage: about 75% for pT1, 50% for pT2, and only 20% for pT3 (3). As previously stated, the key difference between non–muscle-invasive (pT1) and muscle-invasive (pT2) bladder cancer lies in whether the tumor has invaded the muscularis propria (3).

For CIS, the survival rate is 97%, though about half of cases may become invasive within five years if left untreated (3). BCG therapy can greatly reduce this risk, lowering progression to under 10% (3). For localized bladder cancer, the 5-year survival rate is 71% (3). If the cancer has spread to nearby organs or lymph nodes, survival drops to 39%, and for metastatic bladder cancer, the rate is just 8% (3).

One of the greatest challenges in managing NMIBC is understanding and predicting tumor recurrence in patients (16). The relapse rates for NMIBC have been reported to vary between 40% and 90%, depending on the treatment (16). The five-year recurrence rate for low-risk cases is approximately 30–40%, while for intermediate-risk cases it is approximately 45% (16). For high-risk tumors, the chance of returning within a five year span is 60–70% (3). For instance, BCG therapy has been associated with recurrence rates between 43%-59% in other long-term studies (17). Factors impacting disease recurrence in patients include age greater than 65, obesity, smoking, diabetes, tumor size, tumor number, and tumor grade (16). Lastly, various studies have demonstrated that HG tumors and treatment with BCG or pirarubicin are associated with a higher likelihood of the cancer recurring within two years of TUR (17).

## 2. Standard Surveillance Methods

In the following chapter, cystoscopy and urine cytology will be discussed. These are invasive methods to follow up with patients with NMIBC. Topics such as WLC, blue light PDD, NBI, flexible cystoscopy, and TPS for reporting urinary cytology will be reviewed.

### 2.1 Cystoscopy

The diagnostic gold standard in the evaluation of patients suspected of bladder cancer, as well as the monitoring of individuals with a history of NMIBC, are cystoscopy and urine cytology (18). WLC remains the standard technique, and recent technological advancements have significantly improved its image resolution and overall visualization quality (18). Nonetheless, WLC possesses several limitations that impact its accuracy in detecting and staging bladder cancer (18). The inability to accurately detect flat CIS, which is missed in up to 20% of cases, and the difficulty in distinguishing benign lesions from malignancy, particularly in those with prior TUR or intravesical therapy (18), are among these limitations. In addition, cystoscopy is invasive, often uncomfortable, and may cause urinary tract infections, bleeding, or anxiety, which can negatively impact patient compliance with lifelong follow-up protocols (18).

Other invasive techniques such as enhanced cystoscopy which use newer technology like blue light PDD or NBI can locate small or flat tumors that regular cystoscopy might miss (19). PDD is better studied, and the current literature suggests it's better at finding tumors, reducing how much cancer is left after surgery, and lowering the chance of recurrence (19). The EAU and NICE guidelines support using enhanced cystoscopy during TUR (19). The EAU recommends using PDD when cytology is positive, but cystoscopy looks normal (19).

### 2.2 Urine cytology in NMIBC surveillance

Currently, urine cytology is the most commonly used non-invasive test for bladder cancer surveillance (20) . While it's highly sensitive in detecting HG tumors and CIS, its performance in detecting LG tumors is limited (20). Cytological results can also be contaminated by infections or treatment (21)**.**

When performing flexible cystoscopy, urine cytology can serve as an adjunct test to enhance the detection of HG disease (11). With the implementation of TPS when using the system to report urinary tract cytology, it focuses on better identifying HG tumors and understanding that cytology has limitations in diagnosing LG disease (11). Urine cytology is not recommended for follow-up in low-risk and intermediate-risk groups, except for HG/G3 tumors (11). TPS has improved clinical utility in HG disease (11). A systematic review showed that the average proportion of HG malignancy was 40% for atypical urothelial cells, 81% for suspicious cases, and 91% for HG/G3 UC (11).

## 3. Traditional Urinary Biomarkers in NMIBC Follow-Up

This chapter covers urinary biomarkers for NMIBC surveillance and follow-up. Many of these markers, such as NMP22, BTA, UroVysion, and ImmunoCyt/uCyt+, are FDA and EMA approved. Other biomarkers that will be mentioned include CSTB, SVV, and UBC Rapid. Finally, a biomarker combination to enhance the sensitivity of tumor detection will be discussed as well.

### 3.1 NMP22, BTA, UroVysion, ImmunoCyt

Research has shown that the cost of NMIBC follow-up is high, particularly due to the necessity of repeated cystoscopies. However, the costs are further exacerbated by recurrences and progression (21). If urinary markers that are sensitive, specific, and reliable can safely reduce unnecessary procedures, they can help reduce the long-term healthcare costs associated with NMIBC (21). NMP22, BTA, UroVysion, and ImmunoCyt/uCyt+ are assays that have been approved by the FDA and EMA (20). Furthermore, recurrence rates have been associated with newer molecular biomarkers, such as CSTB (22), while others, such as SVV and UBC Rapid, demonstrate potential as urinary tumor markers in ongoing surveillance (23, 24).

A large systematic review of FDA-approved urinary biomarkers like quantitative NMP22, qualitative BTA, FISH, and ImmunoCyt demonstrated moderate diagnostic accuracy, with sensitivities ranging from 0.57-0.82 and specificities from 0.74-0.88 (25). Nevertheless, these discoveries yield only minor modifications in post-test probability and do not substantiate the replacement of cystoscopy in NMIBC surveillance, particularly for LG tumors where biomarker sensitivity remains subpar (25). Biomarkers are more effective

for the initial diagnosis of HG disease and in symptomatic patients; however, they may miss up to 43% of cancers and produce false positives in 12–26% of patients without disease (25). The review emphasized that combining biomarkers with urinary cytology improves sensitivity but still fails to detect around 10% of bladder cancers (25).

UroVysion detects aneuploidy of chromosomes 3, 7, 17, and 9p21 loss, providing objective genetic insights (26). Numerous studies have demonstrated that it is more sensitive than urine cytology, particularly in patients with HG tumors and those who have suspicious cytology but negative cystoscopy findings (26). In a 2008 meta-analysis by Hajdinjak, it was reported that UroVysion displayed a sensitivity of 72% and specificity of 84% compared with 42% and 96% for cytology respectively (26). For example, the detection rate of recurrence during follow-up was elevated as a result of consecutive UroVysion testing (26). Additionally, a higher risk of recurrence and progression has been linked to UroVysion positivity following BCG therapy (26). Recent methodologies are designed to enhance its diagnostic accuracy by incorporating it with miRNA panels, DNA methylation profiling, or TPS-based cytology reclassification (26). UroVysion is not yet cost-effective for routine surveillance; however, it is a valuable risk-stratification tool for selected high-risk NMIBC patients (26).

Preoperative elevations of NMP22 and CSTB have been independently associated with postoperative recurrence in retrospective studies (22). The combined use of NMP22 and CSTB demonstrated greater predictive accuracy than either marker alone, with studies showing their combined use possessing 92.59% sensitivity and 91.18% accuracy, suggesting a role for integrated biomarker testing in follow-up planning (22).

Recent evidence also supports the role of SVV, BTA, and NMP22, with studies showing that their combined use with cytology improves diagnostic performance (23). SVV, BTA, and NMP22 are also supported by recent evidence, as studies have demonstrated that their combined use with cytology enhances diagnostic performance (23). In a single study, the combination of SVV, BTA, and cytology demonstrated a specificity of 96%  a sensitivity of 67% and NPV of 78% for the detection of bladder cancer (23). This suggests that it is a promising approach to more personalized surveillance, particularly in patients with

inconclusive cystoscopy or cytology results (23). Additionally, NMP22 was the sole marker that was significantly correlated with tumor recurrence and grade, thereby substantiating its prognostic significance in the NMIBC follow-up (23).

The potential to improve detection, particularly for HG disease, has been demonstrated by the combination of NMP22 and UBC Rapid (24). For instance, bladder wash cytology was combined with UBC Rapid to achieve a 100% sensitivity for HG recurrence, despite the fact that the sensitivity for LG tumors was limited to 50% (24).

**4. Emerging Urinary Biomarkers**

Research has shifted its attention to non-invasive, accurate, and patient-friendly alternatives for NMIBC follow-up as the limitations of traditional cystoscopy and cytology become more apparent. The potential to decrease the frequency of invasive procedures while maintaining a high standard of cancer surveillance is presented by emerging urinary biomarkers and novel molecular tests. This section outlines several of the most promising developments. We will discuss and highlight the strengths and limitations of tests like Xpert Bladder Cancer, ADXbladder, Bladder EpiCheck, Uromonitor, and Cxbladder.

In the last few years, several novel UBTs have been developed for the non-invasive surveillance of NMIBCs with the same goal of reducing the need for frequent cystoscopies in the monitoring of patients (20). Tests such as Xpert Bladder Cancer, ADXbladder, Bladder EpiCheck, Uromonitor, and Cxbladder have shown promising diagnostic performance, particularly in detecting recurrences of HG tumors (20).

A large comparative analysis found that novel UBTs outperformed traditional FDA-approved markers like NMP22 and BTA (20). These newer tests showed higher sensitivity and NPV (20). Other studies have also backed the high NPV which are over 95% in numerous instances, of some of these novel UBTs (21). The Uromonitor biomarker demonstrated an NPV of 96% and an AUC of 0.924 for the detection of recurrence in NMIBC(20). Most importantly, the use of these tests was found to have the ability to potentially prevent up to 740 unnecessary cystoscopies per 1,000 patients, reducing both patient burden and healthcare costs associated with the follow-up of NMIBC (20).

In a real-world clinical study, the disclosure of Cxbladder Monitor results resulted in a 23.9% decrease in diagnostic tests and procedures, with a 31.1% decrease in flexible cystoscopies (27). In a prospective study, the Cxbladder Monitor outperformed FDA-approved tests such as cytology, demonstrating sensitivity within the range of 82-100% across all tumor stages and grades (28). It achieved 84% sensitivity for LG tumors and 97–100% for HG and post-BCG tumors (28). In a real-world clinical audit, it demonstrated a sensitivity of 91–95% and an NPV of 96–97%, safely allowing patients in the low and high-risk groups to skip scheduled cystoscopies without compromising the detection of HG recurrence (29). In fact, the recurrence rate was 16.2 times lower in Cxbladder Monitor-negative patients, supporting its value as a reliable rule-out tool (29). This test worked well on its own which enabled tailored cystoscopy schedules that cut the number of procedures by 39% for patients with low-risk Cxbladder Monitor results and reduced the use of cystoscopies and CT scans by almost 40% while still effectively detecting bladder cancer (27). It demonstrated longitudinal clinical utility by further reducing test orders such as for example, 77% fewer cystoscopies, and demonstrating a growing physician confidence in its safety, as evidenced by repeat negative results (27). In contrast, the test's capacity to facilitate the escalation of care in patients at a higher risk was demonstrated by the fact that positive results prompted more intensive diagnostic workups (27).

These results substantiate the integration of the Cxbladder Monitor into NMIBC surveillance, which is consistent with the principles of precision medicine and provides a practical solution to reduce the number of invasive procedures in carefully selected patients (27). Its high NPV allows clinicians to safely avoid cystoscopy in patients with a negative result, allowing it to serve as a rule-out test (28). Nevertheless, the necessity for further validation and cost-effectiveness studies prior to widespread adoption is underscored by the current absence of universal guideline endorsement and cost considerations (27).

### 4.1 Novel DNA methylation assays

Recently, a surge in research on urinary biomarkers has expanded the options for non-invasive NMIBC surveillance (30). Novel assays targeting DNA methylation, like GHSR/MAL, Bladder EpiCheck, urinary exosomes such as miRNA-96-5p, miR-93-5p, and mRNA panels Xpert BC

Monitor and CxBladder, have shown NPV values over 90%, particularly for HG tumors, making them strong candidates to safely reduce the frequency of cystoscopy (30). Many of these tests such as ADXbladder, Oncuria, CxBladder Resolve, outperform cytology and improves sensitivity while maintaining specificity, and some studies demonstrate its usefulness in predicting BCG therapy response or early recurrence (30). Their implementation may enhance patient compliance, reduce procedural morbidity, and facilitate personalized follow-up schedules based on molecular risk profiles (30). The integration of such tools aligns with modern NMIBC management goals: precision medicine, patient comfort, and cost-effectiveness (30).

In addition, the Xpert BC Monitor test demonstrated a high NPV of 96.5% overall and 99.7% for HG tumors, along with a sensitivity of 92.3% for HG recurrences, in a prospective cohort of 500 patients (31). The test demonstrated a significantly higher sensitivity than cytology alone in a large study of over 1,000 patients (52.4% vs. 17.9%), particularly for HG tumors with an overall 80.9% sensitivity(31). Additionally, the test had a NPV of 89.2% (32). Despite the fact that its specificity of 78.4% was lower than that of cytology, the combination of both tests enhanced the overall diagnostic performance and enabled the potential extension of intervals between cystoscopies (32). These findings support its application as a rule-out test, particularly in intermediate- and high-risk patients with a high cystoscopy burden (31). In comparison to cytology, the Xpert BC Monitor was more precise and less subjective (31). In the post-pandemic landscape, where patient contact minimization is valuable, the safe reduction of cystoscopy frequency without compromising recurrence detection may be achieved by incorporating this biomarker into follow-up protocols (31). Additional economic assessments will facilitate the determination of its cost-effectiveness and the expansion of its application in clinical pathways (31).

### 4.2 ATR-FTIR spectroscopy, ADXbladder and Bladder EpiCheck

In this section , ATR-FTIR spectroscopy is presented as a novel noninvasive tool for NMIBC surveillance. Additionally, ADXbladder, an ELISA-based technique that can detect MCM5 and bladder EpiCheck, a novel biomarker that shows promising results in studies, will also be reviewed**.**

ATR-FTIR spectroscopy has demonstrated potential as a non-invasive tool for NMIBC surveillance by employing a novel approach (33). By utilizing machine learning models, the method achieved an AUROC of 0.92 and a sensitivity of 86% and a specificity of 77% by analyzing urine samples without the need for preparation (33). The spectral region (2800–3000 $cm^{-1}$) that is most strongly associated with recurrence is corresponding to lipid hydrocarbon chains, which is consistent with the known changes in lipid metabolism in NMIBC (33). Although additional validation in larger cohorts is still necessary, this method offers a patient-friendly, rapid, and promising alternative to cystoscopy that has the potential to be integrated into future follow-up protocols (33).

While urine cytology is highly specific in the follow-up of NMIBC, as previously mentioned, it is characterized by low sensitivity, particularly for LG tumors (34). Recent research has assessed ADXbladder, a urinary biomarker that detects the MCM5 protein and is based on ELISA (34). ADXbladder exhibited a significantly higher sensitivity of 52% in a large multicenter trial compared to that of cytology 17%, including for LG (65%) and HG (59%) recurrences (34). It also demonstrated a specificity of 66.4 % and NPV of 92% (34). ADXbladder has also shown the ability to exclude LG and HG NMIBC recurrence in 97.1% of cases (34). Unlike cytology, which frequently produces non-diagnostic or atypical results that necessitate expert interpretation, ADXbladder delivers objective, clear results quickly within three hours (34). The ADXbladder is a promising non-invasive adjunct or replacement for cytology in NMIBC surveillance, potentially reducing reliance on cystoscopy and improving patient experience, due to its ease of implementation (34).

Additionally, the Bladder EpiCheck test offers a biomolecular marker test (35). In a study of 243 NMIBC patients, it demonstrated higher sensitivity than cytology, 62.3% vs. 33.3%, and strong specificity of 86.3%) and NPV (82.9% vs 75.8%) (35). Although its sensitivity was lower than in earlier validation studies, likely due to real-world variability, its sensitivity for detecting HG tumors was 83.3% and that of LG tumors 46.1 % (35). When combined with cytology, sensitivity improved further up to 90% for HG tumors 56.4 % for LG tumors and NPV of 84.5% highlighting its potential role in reducing cystoscopy frequency, especially in low-risk patients (35).

### 4.3 3-gene DNA-based, mRNA and miRNA assays

In this chapter, promising gene DNA-based biomarkers such as TERT, FGFR3, and OTX will be highlighted. Then mRNA-based biomarkers and their potential in NMIBC surveillance will be covered. Lastly, the topic of exosomal miRNA biomarkers, such as miRNA-21–5p and miRNA-Let-7i-3p, will also be reviewed.

Recent prospective studies continue to explore the integration of urinary molecular biomarkers into the follow-up of NMIBC, especially in high-risk patients (36). The recurrence detection capability of a 3-gene DNA-based assay (TERT, FGFR3, OTX1) was demonstrated to have a 75% sensitivity and 70% specificity in a multicenter validation (36). This assay demonstrated good anticipation, predicting recurrence in patients with a 3.5-fold increased risk even when their cystoscopy was negative (36). The authors propose that diagnostic interventions, such as blue light cystoscopy or biopsy, may be initiated earlier or more effectively in response to positive test results (36). Meanwhile, negative test results might support extending follow-up intervals, particularly when supported by repeat testing or in combination with other risk factors (36).

Other studies have investigated the performance of modern urinary assays, such as the XBCM mRNA-based test, in NMIBC follow-up (37). In a prospective cohort of 301 cases, XBCM demonstrated greater sensitivity, 58% and NPV of 92% than urine cytology with 27% and 87%, respectively particularly for HG tumors (74% sensitivity) (37). However, XBCM's specificity of 89% was lower than that of cytology (97%), and its positive predictive value remained a modest 51% (37). This conclusion validates its potential application in risk-stratified follow-up to inform decisions such as early TUR or intensified surveillance (37).

In another study assessing SVV, hTERT, and KRT7 mRNA in urine samples, promising sensitivity and specificity were found in detecting both LG and HG NMIBC (38). An additional investigation evaluated the mRNA of SVV, hTERT, and KRT7 in urine samples and detected both LG and HG NMIBC with promising sensitivity and specificity (38). Individually, each marker outperformed urine cytology, particularly for early-stage disease (38). Most prominently, the combined expression of all three genes yielded 100%

sensitivity and NPV (38). These results indicate that multi-marker urinary assays could be a beneficial addition to NMIBC follow-up, as they could reduce the need for invasive cystoscopy while preserving high diagnostic accuracy (38).

Genetic background variations, particularly SNPs, play a role in predicting susceptibility, recurrence, or progression in bladder cancer (39). GWAS and exosomal profiling provide a potential path toward personalized surveillance (39). For example, exosomal miRNAs, such as miRNA-21–5p and miRNA-Let-7i-3p, have been associated with chemotherapy resistance and could indicate tumor recurrence before visible lesions appear (39). Similarly, FGFR mutations, already used to guide therapy in MIBC, may have utility in identifying NMIBC patients who are more likely to progress (39). Including genomic and exosomal biomarkers in follow-up may allow for risk-adapted surveillance, especially for high-risk NMIBC patients (39). This information is especially beneficial in situations where patients are hesitant to undergo frequent invasive cystoscopies (39). With further validation, such markers could be integrated into follow-up protocols to complement existing tools and improve early detection of recurrence (39).

### 4.4 Urinary Ln-γ2 chain monomer, genetic and tumor markers

This section will discuss the Ln-2 chain monomer as a potential biomarker and the latest research on its accuracy. Then, prospective tissue markers like HER2 and c-KIT will be reviewed as well as how they can be incorporated into patient surveillance and treatment in NMIBC. In addition, other tissue markers like REG1A expression, Claudin 7 loss, and the Ki-67 proliferation index will be discussed. Finally, other novel molecular biomarkers like TIP30 and the role the PI3K/Akt/mTOR pathway can play in the follow-up of NMIBC will also be highlighted.

A study by Kamada et al. which looked at the urinary Ln-γ2m/uCRN marker, found that it was as reliable or even better than markers like the NMP22 and BTA, especially for detecting LG NMIBC (40). The AUC of Ln-γ2m/uCRN was 0.725 for LG and 0.737 for HG NMIBC, whereas NMP22 was less accurate in LG disease (AUC 0.696) (40). Additionally, based on 3 different criteria, Ln-γ2m/uCRN sensitivity and specificity ranged from 50.4-81.3% and 44.1-87.1% respectively (40). Urine cytology, for example, showed only 11.4% positivity in this study's NMIBC population, highlighting its limited

utility in LG surveillance (40). Importantly, combined use of Ln-γ2m and NMP22 was proposed to enhance sensitivity by compensating for the limitations of each marker individually (40).

Tissue markers like HER2 and c-KIT have shown valuable prognostic potential to help guide follow-up strategies in NMIBC (41). In one prospective study, researchers found that overexpression of both of these proteins was significantly associated with increased risk of recurrence and progression of bladder cancer, especially in HG tumors (41). Patients without detectable HER2 or c-KIT had a 92% likelihood of remaining recurrence-free, while those with strong expression had significantly higher recurrence and progression rates (41). These findings suggest that protein expression analysis before patients undergo their first TUR could be used to tailor follow-up intensity afterwards and can help identify individuals who may benefit from closer surveillance or earlier radical intervention (41). In particular, HER2 overexpression was consistently linked to more aggressive disease, raising the possibility of using anti-HER2 targeted therapies in select patients (41). Similarly, other studies have shown that p53, p63, and HER2 expression levels in tumor tissue strongly correlate with tumor grade (42). Overexpression of p53 and HER2 was significantly associated with HG UC, while p63 was discovered to be associated with LG tumors (42).

Additionally, some tissue-based biomarkers evaluated at the time of initial diagnosis have shown considerable promise in predicting recurrence and survival in NMIBC. Recent studies have highlighted that REG1A expression, Claudin 7 loss, and a high Ki-67 proliferation index can serve as indicators of poor disease prognosis (43). REG1A, a protein involved in tissue regeneration, has a strong correlation with tumor progression and shorter time interval in recurrence-free survival in UC (43). Next, researchers have discovered that Claudin 7, a tight junction protein crucial for epithelial integrity, is downregulated in patients with tumor recurrence, suggesting that this protein can play a vital role in maintaining the barrier function of the urothelium and inhibiting cancer spread (43). Lastly, a high Ki-67 index, which reflects increased tumor cell proliferation, showed a strong correlation with Claudin 7 loss and poor prognosis in patients (43). Crucially, these non-invasive markers can be assessed during initial TURBT specimen collection and

may help identify patients who will require closer surveillance, more frequent cystoscopy, or even consideration for early radical treatment later (43). Together, they offer valuable insights for clinicians to develop a risk-based follow-up strategy in NMIBC patients (43).

Molecular biomarkers like TIP30 also offer new possibilities for refining risk stratification in NMIBC (44). TIP30, a tumor suppressor gene involved in apoptosis and tumor growth inhibition, has shown reduced expression in HG and invasive bladder cancers (44). Studies have demonstrated a correlation between low TIP30 expression and poorer overall survival, as well as higher rates of disease progression ($t=2.63$, $P<0.05$) (44). While TIP30 is not yet used in clinical follow-up guidelines, it may become valuable in future protocols by helping identify patients at greater risk who might benefit from more intensive surveillance while allowing de-escalation in lower-risk cases (44).

The PI3K/Akt/mTOR pathway has been implicated in bladder tumorigenesis, with mTOR activation being more prominent in superficial, non-muscle invasive lesions (45). Recent studies demonstrate that p-mTOR expression is frequently localized to the superficial layers of NMIBC and is lost as tumors progress to muscle-invasive stages (45). This evidence suggests that mTOR signaling plays a role in early tumor growth and may predict recurrence risk (45). Indeed, Fahmy et al. identified mTOR pathway activation as a potential predictor of recurrence in high-risk NMIBC (45). Given this, p-mTOR expression may be explored as a molecular biomarker to identify patients at higher risk for recurrence and as a potential target for adjuvant therapy in NMIBC follow-up protocols (45).

### 4.5 β-catenin, SKP2, ALDH1 and heat shock proteins

In this section, there will be an overview of β-catenin and SKP2 and their value in patient surveillance. Next, we will discuss ALDH1 as a potential biomarker, followed by a review of heat shock proteins such as HSPB2 and HSPB3. Their biphasic role in NMIBC and MIBC will also be contrasted.

Recent evidence also suggests that markers such as β-catenin and SKP2 may offer prognostic value in NMIBC (46). Aberrant nuclear and cytoplasmic β-catenin expression

has been associated with higher tumor grade and stage (T1), potentially indicating tumors with greater invasive potential (46) Similarly, SKP2 overexpression correlated with poor prognostic features in NMIBC, including higher grade and stage, and was not seen in muscle-invasive cases (46). These findings highlight their potential utility in risk-adapted surveillance strategies, where patients with high β-catenin or SKP2 expression might benefit from more intensive follow-up schedules (46).

For the prediction of recurrence and progression in NMIBC, ALDH1 has emerged as a promising biomarker (47). In studies, ALDH1 expression is associated with aggressive tumor characteristics, such as increased grade, greater invasion depth, and the occurrence of concomitant CIS (47). Its presence in TUR specimens, even in the absence of deep muscle sampling, may help stratify patients into higher-risk groups (47). The findings may support decisions for intensified surveillance or earlier intervention. Incorporating ALDH1 into routine evaluation could refine current follow-up strategies and aid in the development of targeted therapies (47)

Recent findings also indicate that heat shock proteins HSPB2 and HSPB3 may have a biphasic role in bladder cancer (48). In non-muscle invasive tumors, diminished expression of these molecular chaperones is significantly correlated with an increased risk of recurrence after TUR (48). Their downregulation may hinder immune responses to BCG therapy and facilitate early relapse (48). In contrast, in muscle-invasive tumors, the overexpression of HSPB2/B3 correlates with chemoresistance and diminished overall survival (48). The results favor HSPB2 and HSPB3 as potential prognostic biomarkers and therapeutic targets, highlighting their significance in the stratification and monitoring of NMIBC patients (48).

### 4.6 Urinary proteomics and metabolomics

In this section, the topics of urinary proteomics and metabolomics will be covered. First, proteomics and its role in cancer diagnostics, surveillance, and treatment will be highlighted. Then two promising biomarkers, APOL1 and ITIH3, which have been identified by proteomic analysis, will be mentioned. Finally, other potential biomarkers that can be detected by these techniques will be briefly discussed.

Proteomics is the large-scale study of proteins, studying how they work, interact, and how they change in different diseases (49). To study proteins, scientists use different tools and techniques, like separating proteins by size or charge, identifying them using mass spectrometry, and analyzing how proteins interact with each other (49). Such diagnostic methods can be used to compare healthy and diseased cells, locate new protein targets for drug research and lead to the discovery of new biomarkers for diagnosing diseases (49).

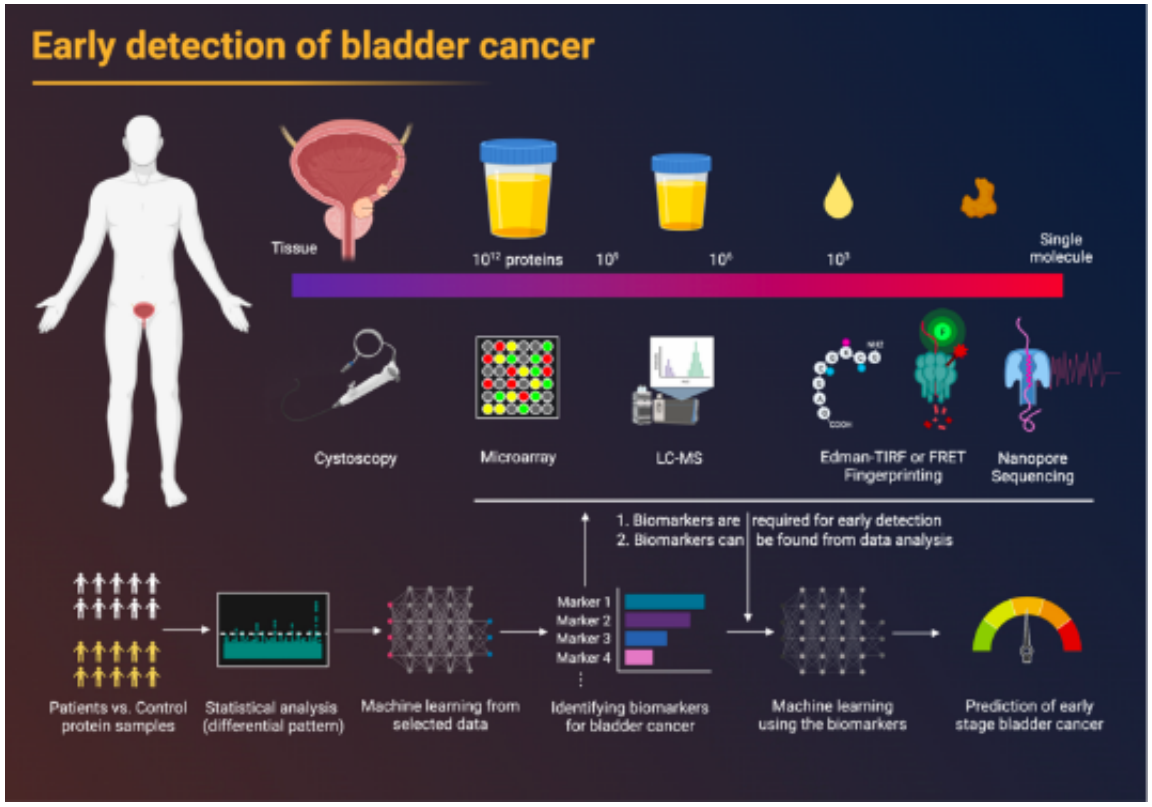


Image: Showing how proteomics can help detect bladder cancer using different techniques (50).

An emerging tool in the non-invasive follow-up of NMIBC is urinary proteomics (51). Two proteins, APOL1 and ITIH3, were identified as potential biomarkers for bladder cancer detection in a recent study that employed LC-MS to analyze urine samples (51). In contrast to HC, both proteins exhibited elevated levels in the urine of patients with UC, indicating their potential for identifying malignant from benign conditions (51). APOL1,

which is involved in the regulation of autophagy and lipid transport, has been associated with a variety of other cancers and may contribute to the proliferation and invasion of bladder tumors (51). ITIH3, which is a carrier of hyaluronic acid, is also associated with multiple cancers and inflammation (51). These discoveries are consistent with the biological characteristics of bladder cancer, which include the activation of the ferroptosis and ERK/MAPK signaling pathways (51). Although still in the experimental phase, these biomarkers demonstrate potential for non-invasive recurrence monitoring. potentially reducing reliance on invasive cystoscopy (51). Further validation in multicenter trials and recurrence-monitoring cohorts is needed to confirm clinical utility (51).

Furthermore, a study employed LC-MS/MS to identify eight candidate proteins and develop diagnostic models that significantly outperformed conventional urine cytology (52). Their panel exhibited AUROCs of 0.827–0.851 when combined with cytology, indicating a high level of clinical potential (52). The selected proteins, which include CDC5L, ITIH2, AFM, APOA1, and FGB, have exhibited differential expression in bladder cancer and may be indicative of tumor biology and recurrence risk (52). This method advocates for a transition to personalized surveillance strategies that are based on urine, which has the potential to decrease the necessity of invasive cystoscopies in certain patients (52).

## 5. Imaging: CT virtual cystoscopy, multiparametric MRI molecular imaging & photoimmunotherapy

In this chapter, the role of imaging modalities in the surveillance of NMIBC will be reviewed. CT virtual cystoscopy and its ability to detect tumors will be discussed. Then newer modalities will also be mentioned, like mpMRI and PIT, which detect tumors using fluorescent tracers. Lastly, established modalities, like T2-weighted imaging, DWI, and DCE, will also be mentioned**.**

CT Virtual cystoscopy is a promising diagnostic method that uses thin-slice CT and air or contrast filling to produce a three-dimensional image of the bladder (53). Although virtual cystoscopy is unable of replacing standard cystoscopy due to its inability to detect mucosal color changes and lower sensitivity in detecting smaller lesions, recent studies have

reported excellent anatomic visualization and high sensitivity for tumors exceeding 5 mm (53). A study that employed 16-MDCT discovered that it had a sensitivity of 75% for the detection of small lesions and identified 20 of the 23 tumors that were confirmed by conventional cystoscopy (53). These results indicate that virtual cystoscopy may have a potential application in low-risk NMIBC patients, where it could be employed in a safe manner, lengthen follow-up intervals between standard cystoscopies, improving compliance while reducing cost and invasiveness (53).

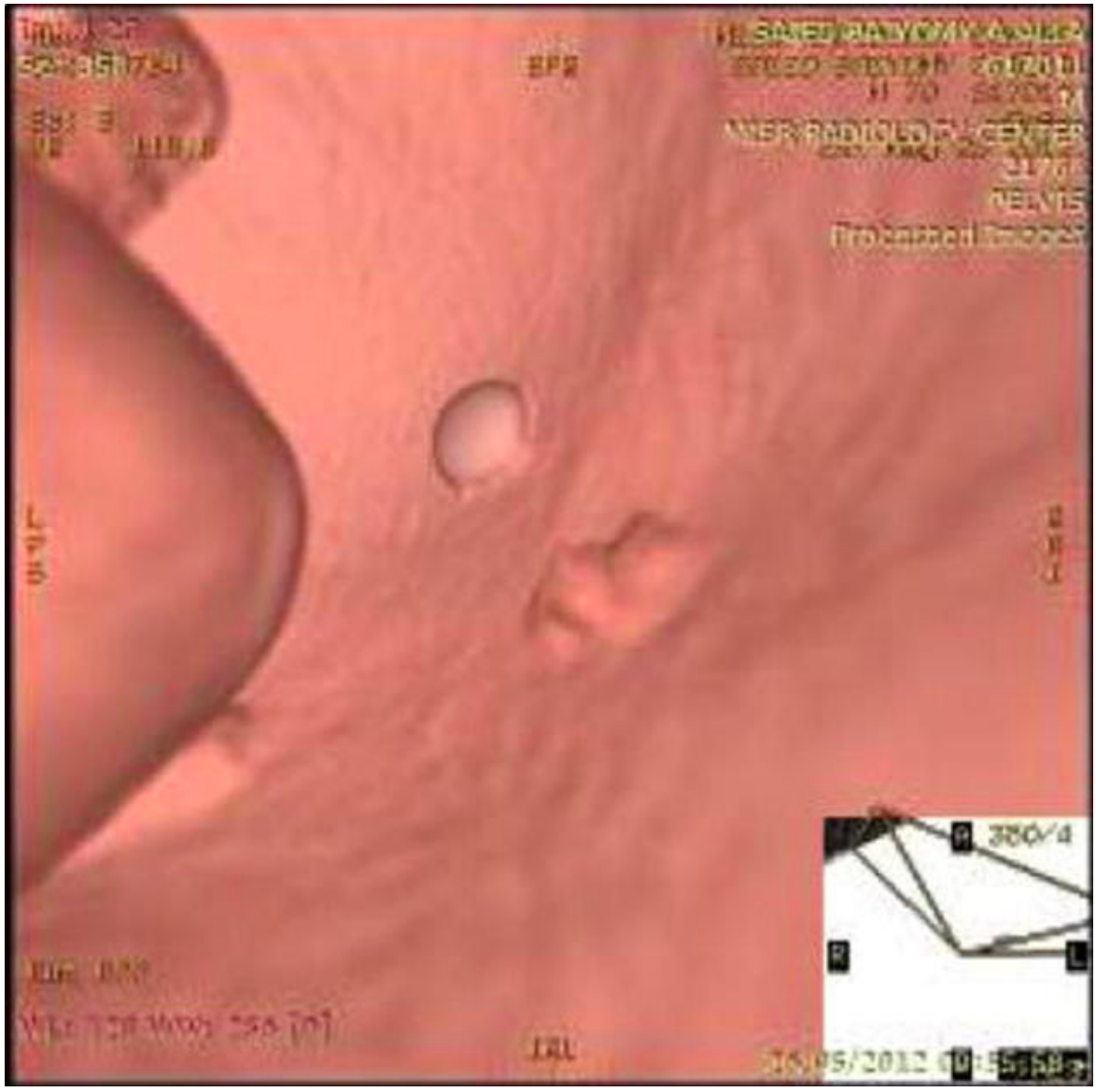

Image: Virtual cystoscopy of a 70-year-old man with two recurrent lesions at their first follow-up (53)

Imaging plays an increasingly important role in the follow-up of NMIBC, both to evaluate local recurrence and upper tract involvement (54). Techniques such as mpMRI offer non-invasive alternatives for selected patients (54). In the differentiation of NMIBC from MIBC, mpMRI, particularly with T2-weighted imaging, DWI, and DCE DCE, exhibits a high degree of accuracy (54). MRI interpretation is standardized by tools such as the VI-RADS scoring system, which may assist in the formulation of treatment decisions (54). Even though MRI is not yet a viable alternative to cystoscopy due to its cost, accessibility, and inability to detect flat lesions such as CIS, it can be still be a valuable adjunct in follow-up protocols with patients, particularly when upper tract imaging is also required (54).

In recent years, innovative methods such as PIT and endoscopic molecular imaging have demonstrated potential (55). These methods employ fluorescent tracers that target tumors to enhance the detection of small, occult lesions and to provide real-time intraoperative feedback during TUR(55). Studies demonstrate that molecular imaging can more accurately identify surgical margins and tumor depth than white light alone, potentially reducing residual disease and recurrence (55).

Additionally, NIR-PIT, which employs monoclonal antibodies that are linked to photosensitizers that are activated by, has the ability to selectively destroy tumor cells with minimal toxicity to healthy urothelium (55). Preclinical studies have shown promising results when PIT is used to target CD47, EGFR, and HER2 in bladder cancer models (55). A diffuser attached to the tip of a fiber optic probe can be used to evenly disperse NIR light along the bladder wall after it is administered through a cystoscope (56). NIR-PIT has the ability to eliminate superficial tumors and CIS lesions as well as residual deeper cancer cells that remain exposed after tumor debulking, with a tissue penetration depth of up to 2 cm (56). Although these technologies are still in the early stages and are still considered "invasive," they have the potential to improve tumor visualization and resection, reduce the need for frequent follow-up cystoscopies, and improve adjuvant treatment outcomes (55). If validated through larger clinical trials, these innovations could redefine follow-up protocols, integrating precision diagnostics and targeted therapy to reduce recurrence rates while minimizing treatment burden (55).

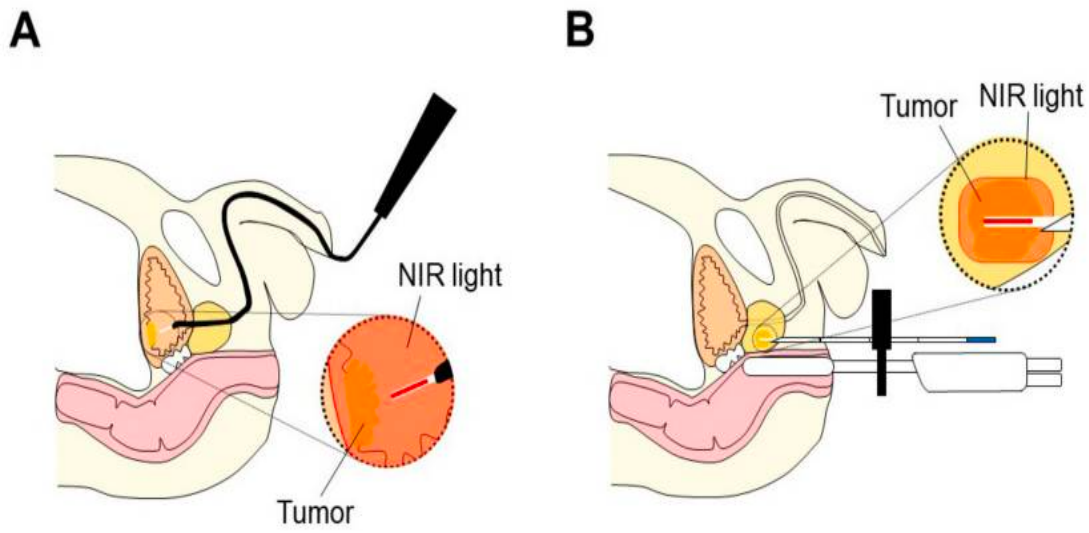


Image: A: NIR light is irradiated to a bladder tumor using a cylindrical diffuser via a cystoscope; B: NIR light is irradiated to a prostate tumor using a cylindrical diffuser via a needle (56)

**6. Risk Stratification Tools**

In this chapter, the EORTC and CUETO models and scoring system will be discussed. This section will discuss their use in NMIBC monitoring, clinical application, and limitations.

The 2006 EORTC scoring model should be used to estimate the risk of recurrence in patients not treated with BCG (3). The 2016 EORTC model which is based on 1–3 years of maintenance)or the CUETO risk model, itself based on 5–6 months of therapy, is strongly recommended for patients treated with BCG to assist in the prediction of recurrence risk on an individual basis (3).

The EORTC and CUETO are still widely used in NMIBC to predict recurrence or progression and to guide follow-up intensity (57). Nevertheless, external validations have demonstrated that these models frequently overestimate risk, particularly in patients who have received BCG treatment (57). To improve the precision of these models, recent projects have incorporated molecular and genetic biomarkers (57). The predictive power of EORTC scores, for instance, was enhanced by MIB-1 expression and the presence of FGFR3 mutations (57). In addition to FISH, p53, SVV, IL-2, and DDR gene alterations,

other biomarkers have demonstrated the potential to predict BCG response or recurrence using these scoring systems (57). These results underscore the increasing significance of biomarker-informed surveillance strategies, which facilitate a more personalized, risk-adapted approach to NMIBC follow-up (57). This approach has the potential to lower the number of unnecessary procedures and enhance the detection of high-risk patients (57).

In order to customize the intensity of follow-up for patients with NMIBC, it is imperative to conduct precise risk stratification (58). A recent validation study of the EAU, EORTC, and CUETO risk algorithms confirmed their moderate performance in predicting recurrence and progression (58). EORTC performed slightly better than CUETO, particularly in patients who did not receive immediate postoperative chemotherapy (58). Nevertheless, the c-index values of even the most successful models like EORTC are low, suggesting that their predictive accuracy is limited (58). These tools also lack external validation for real-world clinical use and fail to account for individual factors, such as surgeon variability or BCG maintenance strategies (58). Consequently, their effectiveness in determining the frequency or intensity of follow-up is limited (58). The results corroborate the EAU Guidelines Panel's request for updated or new predictive tools that may incorporate molecular, immune, or inflammatory biomarkers in order to enhance prognostic accuracy and facilitate customized surveillance strategies in the management of NMIBC (58).

| FACTOR | RECURRENCE | PROGRESSION |
|---|---|---|
| **NUMBER OF TUMORS** | | |
| Single | 0 | 0 |
| 2-7 | 3 | 3 |
| >8 | 6 | 3 |
| **Tumor diameter** | | |
| < 3 cm | 0 | 0 |
| > 3 cm | 3 | 3 |
| **Prior recurrence rate** | | |
| Primary | 0 | 0 |
| < 1 recurrence/year | 2 | 2 |
| > 1recurrence/year | 4 | 2 |
| **Category** | | |
| Ta | 0 | 0 |
| T1 | 1 | 4 |
| **Concurrent CIS** | | |
| No | 2 | 2 |
| Yes | 4 | 2 |
| **Grade (WHO 1973)** | | |
| G1 | 0 | 0 |
| G2 | 1 | 0 |
| G3 | 2 | 5 |
| Total score | 0-17 | 0-23 |

Table: NMIBC recurrence and progression scores (59)

**7. Active surveillance and follow up in specific patient groups**

This chapter will cover AS strategies, emphasizing their ability to optimize and enhance follow-up in NMIBC patients. The Uromonitor test, which can enhance surveillance and reduce the need for invasive follow-up procedures, will also be highlighted. Next, this chapter will discuss a

special patient group, pediatric NMIBC, and the monitoring techniques. Lastly, the CCI score and its predictive value will also be highlighted

Surveillance strategies, not just biomarkers, can play a major role in reducing the need for invasive follow-ups of patients. Optimizing biomarker use, time intervals between visits, and taking a more proactive role with patients can improve the diagnostic accuracy of non-invasive surveillance in NMIBC patients.

The Uromonitor test is a urine-based assay that is anticipated to detect bladder cancer recurrence and is a promising non-invasive alternative for NMIBC surveillance (60). A recent clinical study that assessed Uromonitor in patients with pTa LG NMIBC demonstrated a high level of diagnostic accuracy, with a NPV of 98.8%, a specificity of 96.2%, and a sensitivity of 89.7% (60). It is important to note that the test could have prevented up to 87% of unnecessary cystoscopies and 42% of TURs when used as a first-line screening tool during surveillance (60). These findings indicate that Uromonitor has the potential to increase patient comfort and potentially reduce healthcare costs by reducing the need for invasive follow-up procedures (60). Nevertheless, a longer-term follow-up is still required to verify the false-positive rate and long-term recurrence detection. The integration of Uromonitor into standard follow-up protocols may enable more personalized, risk-adapted surveillance, particularly in low-risk NMIBC patients (60). In selected patients, in-office fulguration or AS can frequently be employed to manage small, LG recurrent tumors (11).

Papillary LG NMIBC tumors have a favorable prognosis and a low risk of progression, as demonstrated by evidence from animal models and long-term human studies (61). This corroborates the viability of AS as a management strategy for patients who have been meticulously selected (61). Clinical studies indicate that AS protocols result in low progression rates, particularly when tumors are small, solitary, and cytology is negative (61). Consequently, the quality of life of low-risk patients may be enhanced, and unnecessary interventions may be reduced through AS (61). For instance, the AS and follow-up of LG NMIBC can be influenced by molecular biomarkers that were previously mentioned, including FGFR3 mutations, NMP22 levels, and Ki-67 (61). During active treatment, these markers can assist in the the stratification of patients, surveillance, and the

potential identification of individuals who require earlier intervention can all be beneficial (61). For example, ucfDNA has shown promise in detecting progression months before visible invasion, offering a powerful tool to refine inclusion, monitoring, and exit criteria in AS (62). Furthermore, they may enhance tumor detection and potentially enhance surveillance accuracy in patients under AS protocols when combined with imaging techniques such as NBI and photodynamic diagnosis (61). According to a recent review, approximately 10–15% of patients experience progression in stage or grade, and up to two-thirds of patients eventually discontinue AS (63). Additionally, the definition of inclusion criteria is inconsistent, and the majority of studies do not employ validated biomarkers or enhanced cystoscopy for patient selection (63). In LG tumors, cytology, which is frequently employed for surveillance, exhibits inadequate sensitivity (63). Although emerging tools such as Bladder EpiCheck and UROseek may facilitate risk stratification, they are not yet adequate to replace cystoscopy (63).

Studies indicate that US may be a good tool for following up in certain population groups, including pediatrics and patients with very low risk (15). Cystoscopy may be required solely when physicians anticipate a recurrence based on the actual US findings (15). For example, one study, monitored pediatric patients with US at specific intervals following surgery and reserved cystoscopy exclusively for those who exhibited signs of recurrence (15). These results support the idea that surveillance strategies in certain bladder cancer cases can be customized based on recurrence risk (15).

Patient-related factors, such as comorbidities, may influence the risk of recurrence in addition to tumor-specific features, thereby guiding follow-up strategies (64). A recent large retrospective study revealed that a higher CCI was independently associated with an increased risk of recurrence after TURBT for NMIBC (64). Despite the adjustment for tumor stage and intravesical therapy, patients with a CCI > 4 exhibited significantly higher hazard ratios for recurrence (64). This discovery reinforces the inclusion of comorbidity burden in risk stratification models and implies that patients with high CCI scores may require more stringent surveillance protocols, particularly given that they are frequently less eligible for radical treatments such as cystectomy (64). The CCI may thus serve as a practical tool to personalize follow-up protocols and optimize outcomes (64).

## 8. Lifestyle and Systemic Markers

This section will discuss lifestyle modifications, such as lifestyle counseling, and their role in patient follow-up in NMIBC. Then, the role of non-urinary biomarkers like systemic inflammatory markers such as the NLR will also be highlighted as a potential monitoring tool for this cancer.

In addition to non-invasive diagnostic tools and emerging biomarkers, lifestyle modifications may also affect the prognosis of NMIBC (65). A prospective study that assessed adherence to the 2018 WCRF/AICR lifestyle recommendations discovered that improved lifestyle scores three months after diagnosis were associated with a decreased risk of first recurrence (65). The potential role of post-diagnosis behavioral changes is underscored by the fact that lifestyle prior to diagnosis did not exhibit any such association. This study implies that a healthy lifestyle may be beneficial in the context of intravesical therapy, such as BCG, as it may reduce tumor reimplantation or enhance immune responses, despite the fact that not all findings reached statistical significance (65). These results bolster the inclusion of lifestyle counseling in NMIBC follow-up strategies, particularly in light of the fact that body weight, diet, and physical activity also influence the health of the cardiovascular system and the risk of secondary cancers in survivors (65).

Recently, systemic inflammation markers have become valuable diagnostic tools for predicting tumor recurrence and progression in NMIBC patients (66). In meta-analysis research, NLR was significantly correlated with both recurrence and disease progression in NMIBC patients who were treated with intravesical BCG after TUR (66). Higher preoperative NLR levels obtained from regular blood tests, are linked to a weakened immune response, resulting in an increase in neutrophils and a decrease in lymphocytes that fight tumors (66). NLR may aid clinicians in customizing the intensity of follow-up, thereby enabling the early detection of recurrence or progression in high-risk patients, as a non-invasive, cost-effective biomarker (66). NLR necessitates additional prospective validation prior to its widespread implementation in clinical protocols, despite its promising potential (66).

Identifying high-risk features using tools such as the NLR may assist in the selection of patients who require closer monitoring or earlier escalated therapy for follow-up (67).

**9. Summary table of Key Urinary Biomarkers**

| Biomarker name | Key Characteristics |
|---|---|
| NMP22 | • FDA and EMA approved<br>• Combined with CSTB demonstrates greater predictive accuracy (91.18%)<br>• Combined sensitivity of 92.59%<br>• Combined with UBC Rapid shows improved detection of HG disease |
| BTA | • FDA and EMA approved<br>• Combined with Survivin and cytology shows a sensitivity of 67%, a specificity of 96% and a NPV of 78% |
| UroVysion | • FDA and EMA approved<br>• UroVysion detects aneuploidy of chromosomes 3, 7, 17, and 9p21 loss, providing objective genetic insights<br>• Sensitivity of 72%<br>• Specificity of 84% |
| ImmunoCyt/uCyt+ | • FDA and EMA approved |
| CSTB | • Combined with NMP22 demonstrates greater predictive accuracy (91.18%)<br>• Combined sensitivity of 92.59% |
| Survivin | • Combined with BTA and cytology shows a sensitivity of 67%, a specificity of 96% and a NPV of 78% |
| UBC Rapid | • Combined with NMP22 shows improved detection of HG disease<br>• Combined with bladder wash cytology shows a sensitivity of 100% for HG recurrence |
| Xpert Bladder Cancer | • Novel UBT<br>• NPV of 96.5% overall<br>• 99.7% for HG tumors<br>• Sensitivity of 92.3% for HG recurrence<br>• Reduction of cytoscopy frequency without compromising recurrence detection may be achieved by incorporating this biomarker into follow-up protocols |
| Adxbladder | • Novel UBT<br>• An ELISA-based technique that can detect MCM5 protein<br>• Outperforms cytology<br>• Specificity of 66.4%<br>• NPV of 92%<br>• Higher sensitivity for LG and HG recurrences (excludes it in 97.1% of cases)<br>• Delivers results in three hours<br>• Promising non-invasive adjunct or replacement for cytology |
| Bladder EpiCheck | • Novel UBT |

| | |
|---|---|
| | • NPV of more than 90% for HG tumors (reduce the frequency of cytoscopy) |
| Uromonitor | • Novel UBT<br>• Biomolecular marker test<br>• NPV of 96%<br>• Sensitivity of 83.3% for HG tumors and 46.1% for LG tumors<br>• Combined with cytology sensitivity improved up to 90% for HG, 56.4% for LG tumors and NPV of 84.5%<br>• Potential to reduce cytoscopy frequency in low-risk patients<br>• AUC of 0.924 for detection of recurrence |
| CxBladder | • Novel UBT<br>• Sensitivity of 82% to 100% across all tumor stages and grades<br>• NPV of more than 90% for HG tumors (reduce the frequency of cytoscopy) |
| Ln-γ2m/uCRN | • AUC of 0.725 for LG<br>• AUC of 0.737 for HG NMIBC<br>• Sensitivity from 50.4-81.3%<br>• Specificity from 44.1-87.1% |
| TIP30 | • Novel UBT<br>• A tumor suppressor gene involved in apoptosis and tumor growth inhibition<br>• Low expression in HG and invasive bladder cancers<br>• Correlation between low TIP30 expression, higher rates of disease progression and poor overall survival |
| PI3K/Akt/mTOR | • mTOR plays a role in early tumor growth and may predict recurrence risk in high-risk NMIBC |

## 10. Conclusion

Precision medicine, personalization of treatment, and patient comfort are the hallmarks of the new era in which NMIBC management is entering. Although cystoscopy and cytology are still essential for surveillance, the burden they impose on patients and healthcare systems emphasizes the necessity of more intelligent, less invasive alternatives. In this regard, emerging biomarkers and imaging technologies provide optimism, as numerous examples demonstrate high diagnostic accuracy and NPV's, particularly for HG disease. However, these tools are not without their limitations, despite their promise. Before they can be widely implemented, numerous of them necessitate additional validation, standardization, and economic evaluation. Additionally, surveillance planning must increasingly take into account individual patient factors, including age, comorbidities, and lifestyle. Ultimately, the future of NMIBC follow-up is dependent on the integration of molecular insight with personalized care, which guarantees that patients are not only monitored effectively but also treated with precision and dignity.

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